

IN THE SPECIFICATION

The specification has been reviewed and terms have been clarified including the ones specifically pointed out by Examiner.

On page 2 please revise the first paragraph under the Heading: "Ion Channel Research" as follows:

[0013] An important area of nerve research concerns the study of ion channels in the membranes of nerve cells that open and close to regulate nerve impulses including ~~include~~ those signaling pain. For heat pain research with nerve cells in vitro, such as experiments concerning ion channels, heat stimuli are typically delivered to cells with a standard perfusion bath apparatus or a Peltier contact heating device. With these devices rates of temperature change are low requiring heat durations on the order of seconds for substantial temperature rises. These instruments can not achieve measurable thermal stimulation of cells in milliseconds. A significantly more rapid stimulus would permit measurements of opening and closing of these channels in response to heat, thereby providing significantly greater insight into the molecular mechanisms of channel activation and regulation.

On page 3 please revise the paragraph Entitled "Use of Lasers" as follows:

It is known to use lasers for producing pain. Lasers operating at various infrared wavelengths have been utilized in pain research. Lasers provide advantages as compared to radiant heat sources. These are:

- high rate of heating,
- heat for some wavelengths can be delivered by optical fiber, and
- ease of directing laser energy to specific locations.

One problem with many laser sources is that skin damage occurs before or simultaneously with the feeling of pain. Another problem is that laser pulses may produce double sensations that can induce potentials on one type of fiber by suppressing interaction mechanisms between other nerve fibers, for example in the spinal cord. This is most frequently seen for laser pulse duration of more than 100 ms. It is known that lasers operating in the range of 980 nm can produce pain in skin tissues. Photons at this wavelength penetrate to about 3.8 mm through skin tissue.

On pages 3 and 4 please revise the paragraph entitled: "Nociceptors: A-Delta Fibers and C Fibers" as follows:

Basic research in pain, analgesia and pharmacology has been accelerating over last several years. One of the results of this work has been the clear demonstration of the differential involvement of different pain sensing nerve cells (called nociceptors). There

are two main classes of pain sensing nociceptors in the skin and other peripheral tissue: myelinated A-delta nociceptors and un-myelinated C nociceptors. These nerve cells may also be called nerve fibers. Sensations evoked by activation of these two different nociceptor types are quite distinct. A-delta fiber mediated pain is typically described as sharp, or piercing. C fiber mediated pain, on the other hand, is usually described as burning or aching. There is also a dramatic difference in the latency to pain after activating these two nociceptor types. For example, a rapid pin-prick to a foot can produce two distinct pain sensations: first, a sharp pain which ends when the pin is removed, followed by a second, burning sensation which may be felt well after the needle has left the skin. The first pain is mediated by A-delta nociceptors, and the second pain is mediated by C fiber nociceptors. Thus, activation of these two nerve types has a different meaning to the body. Numerous physiological, anatomical, and pharmacological distinctions have also been described as being distinct between these two nerve types. For example, morphine is much more effective in inhibiting C fiber mediated pain than A delta fiber mediated pain. Included among these is the finding that, with a constant stimulus, such as a wound, A-delta nerve cells respond robustly at first, but then rapidly become to quiescent. On the other hand, C fibers, with the same stimulus, continue to fire continuously. A delta fibers are usually responsible for mediating of sharp pin prick pain and C fibers for warmth sensations and hot/burning pain.

On pages 15 and 16 please revise the first three paragraphs under the heading entitled: "Laser Configurations" as follows:

A 980-nm diode laser 28 of the type described above can be arranged in a variety of configurations for laboratory research, clinical research, clinical testing or treatment. Some of these configurations are described in FIGS. 1A through 5.

[0087] FIG. 1A shows a system in which a fiber optic 29 is used to deliver laser pulses from diode laser 28 to skin surface 20 with the temperature of the surface being monitored by infrared sensing camera 14 that provides a feedback signal to controller 26 for synchronization of stimulation scan and image recording and monitoring of time interval between applied laser pulse and muscle reflex. FIG. 1B is similar to FIG. 1A except the laser pulses are delivered as a collimated beam using lenses 22. FIG. 1C combines the pulse delivery features of FIGS. 1A and 1B.

[0088] In FIG. 2A an active erbium doped fiber 18 24 is pumped by the 980 nm diode laser system 30 to produce 1450 nm laser pulses at the output of the fiber. The preferred fiber 18 is single mode fiber with core diameter 5-15 microns, NA 0.11-0.22. The 1450 nm pulses are used to illuminate skin surface 20 through optical fiber 29 for applications where this longer wavelength pulse energy is desired. This setup is also good for doing activation of ion channels in laboratory experiments. In FIG. 2B the output from laser diode pumped fiber laser 18 and optical fiber 29 24 is collimated with a tunable collimator

22 to control the diameter of the beam within a range of 1 to 15 microns. An infrared sensing camera 14 in both cases monitors the irradiated spot 20 and records reflexes of the subject.

On page 17 please revise the first paragraph under the heading entitled "Example 1: Pin Prick Pain to Activate A Delta Fibers" as follows:

It is well known that for heat induced simulation of prick-pain stimulation the temperature of the skin has to be more 46-48 C degree and ramp of heating has to be over 70-100 C degree per second. However, these data were based on pulse durations of more than 300 ms. To the best of Applicant's knowledge, there here are not any data in the literature relating absolute temperature and ramp of heating for stimuli duration less than 300 ms. The best, simplest protocol, to access A-delta nociceptors and evoked monomodal pin prick pain is the following:

On page 19 please revise numbered paragraph 6) as follows:

6) For determining the number of pulses that evokes threshold of pin-prick type pain a square waved pulses within a range of pulse duration of 10-300 ms and interstimulus delay of 0.1-3 sec are applied. Examples of repetitive pulse application for A delta stimulation are shown in FIGS. 12 and 13.

On page 34 under the heading "General Algorithms" please revise numbered paragraph 6) as follows:

6) Control Voltage on Input ~~input~~ Pulse Length Timer Stop

(Pulse Length Timer Stop input (TTL, active high)) and input Stop the laser input (shuts down the laser) (TTL, active low) are located on back panel through a separate DB9 connector.

Every command has a description there is described of the aim of the command, parameters that command control and range of parameters i.e. Tmin; Tmax; Step--for pulse duration.

The set of command is for following:

- a) ~~Arbitrary~~ arbitrary shape of pulses
- b) measurement of number of applied pulses for repetitive pulses when lasing is terminated,
- c) measurement of pulse duration of single pulses when lasing is terminated, and
- d) reading all parameters of applied pulses: power, current, pulse shape, pulse duration, interstimulus intervals, trigger pulses delays, power of aiming beam, pulse duration of aiming beam.